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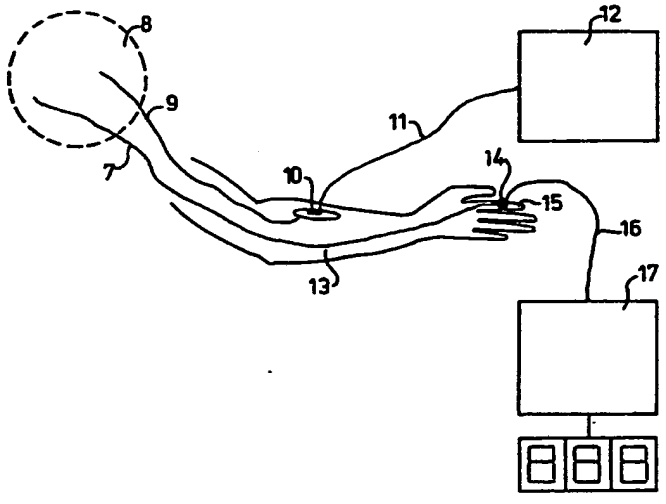

(57) Abstract

System for quantifying the general anesthetic effect of general anesthetics on a human or an animal comprising means (10, 11, 12) for transmitting a series of constant strength stimuli to the input side (9) of the nervous system (7, 8, 9) of the human or animal to evoke time restricted responses at the output side (7) of the nervous system, and means (14, 15, 16, 17) for detecting the evoked responses and for processing corresponding detection signals. By comparing the strength of responses evoked before any anesthetic was administered to the strength of responses evoked during the administering of anesthetic the depth of the resulting anesthesia can be determined unambiguously between 0 and 100 % avoiding thereby an eventual overdose of anesthetic.

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System for quantifying the effect of general anesthetics on a human or an animal.

The invention relates to a system for quantifying the anesthetic effect of anesthetics on a human or an animal, comprising:

- first means for transmitting a predetermined stimulus to the input side of the nervous system of the human or animal,
- second means for activating said transmitting means in a controlled manner,
- third means for detecting the response evoked in the body of the human or animal as result of each transmitted stimulus and for generating a thereto corresponding signal,
- fourth means for processing the signals generated by said third detecting means,

A system of the above indicated type is described in US 4,570,640. This known system is designed to determine the location and depth of blocks of transmission of nerve impulses at the spinal cord level induced by a local anesthetic administered to a human or animal.

The purpose of a local anesthetic is to render a part of the periphal nerves locally insensible so that a block is established between the respective peripheral sensors and the central nervous system. Such a block prevents the transmission of stimuli from the peripheral receptors within a blocked section of the body of the human or animal to the central nervous system, whereas the transmission of stimuli from peripheral recepters in other parts of the body of the human or animal is not interrupted. Stimuli reaching the central nervous system from a non-blocked body part may still evoke a corresponding response in the body.

To obtain information about the location of the border between the blocked body section and the non-blocked body section the US patent 4,570,640 proposes to use an array of stimulation elements, typically electrodes, which are applied on the skin of the human or animal. The array of electrodes comprises on the one hand an elongated row of electrodes which are positioned approximately parallel to the spinal cord and comprises on the other hand a number of reference electrodes which are positioned on

a part of the body, called the reference site, which is certainly not effected by any local anesthetic.

After administering a local anesthetic to the body of the human or animal near the spinal cord the capability of the afferent nerves to transmit stimuli from receptors to the spinal cord will be locally decreased or completely eliminated temporarily. The elongated row of electrodes running across the body site being influenced by the local anesthetic as well as across a further not influenced body site is used to determine the border between both body sections. For that purpose stimuli are applied to the body through the various electrodes in a predetermined order and the eventual responses evoked in the body are detected by an array of sensing means.

As described in column 15 lines 20 and following of US 4,570,540 the purpose of the energy delivery from a stimulator through the array of stimulation elements or electrodes is to deliver energy to stimulate the underlying structure in order to test the nervous system perception of superficial and deep pain sensation at various dermatomal and sclerotomal sites. This includes the site or sites to be tested and one or more reference sites for comparison. A second purpose of the energy delivery is to stimulate the dermatome in order to test the sympatic integrity. This is done by comparing the reactivity pattern in the blocked area to that in the reference site. According to column 16, lines 56 and following the comparator receives the evoked response due to the applied stimulus at the various dermatomal sites to be tested and compares this response against that obtained from the reference site.

The strength of the stimuli that is applied to the reference site should not exceed that which produces a strong sensation to the mild pain sensation and/or should be gradually increased in strength until the evoked response is obtained in order to assure the patient's comfort. On the other hand, however, the strength of stimulus which is applied to the testing site should be equal to that applied to the reference level, 1.5, 2, 2.5 and 3 times as much (column 17, lines 2-6).

If this prior art system is used to test the effectiveness of a local anesthetic then the evoked responses are compared by asking

the patient to determine when the experienced sensation exceeds a certain point. The patient may signal a particular sensation or this signaling may be in the form of the pressing of a control, such as a switch, in a particular fashion (column 17, lines 52-57). Following the injection of local anesthetic solution in a spinal or epidural space the intensity of stimulation will be gradually and progressively increased and will be directed to the dermatomal area close to the site of injection that is likely to be blocked first, and also from time to time will be directed to the reference site for comparison. This process will be continued until a maximum intensity of the stimulus which produces no sensation is reached.

This prior art system is developed to be used exclusively for testing the effect of local anesthetics. The system has to make use of a large number of electrodes which for instance during surgery can be a nuisance. A requirement to obtain a proper indication about the influence of the local anesthetic is that the patient is able to inform the system operator about the strength of the sensation, varying between slight sensation, mild pain and severe pain sensation. This prior art system relies specifically on the proper and normal functioning of the central nervous system by using reference electrodes attached to a reference site of the human or animal body for comparison purposes as explained above.

The depth of the local block, induced by the use of a local anesthetic, is tested by increasing the strength of the stimuli applied to the local test site until, according to the described embodiments, the strength is three times the strength of a stimulus which in a non-blocked section of the body will evoke a response which is bearable for the patient.

If a general anesthetic has to be used the circumstances are completely different. A general anesthetic decreases the ability of the central nervous system to respond on incoming stimuli. Even if both the afferent nerves, transporting stimulus-induced signals to the central nervous system, as well as the efferent nerves, transporting response signals from the central nervous system to effectors, are completely active, eliminating temporary the capability of the central nervous system to receieve and process the incoming stimuli will lead to a condition of complete anaesthesia.

To reach this situation after administering one type of anesthetic the functioning of central nervous system of the human or animal gradually slows down, starting with clear consciousness and going via a decrease in pain perception, amnesia phenomena, loss of spontaneous activity, loss of reactivity on afferent stimuli and loss of motor response ultimately to a "sufficiently deep" anesthesia. During this "sufficiently deep" anesthesia there is no "awareness". However, as soon as the required anesthesia depth is reached the decrease in functioning of the central nervous system may unintentionally be furthered, whereby toxic effects of the anesthetic will lead to a decrease of the breathing function, loss of vasomotoric regulation, complete stop of the breathing function, slowing of the heart function and ultimately even death. Medical science predicts that, as soon as a general anesthesia of sufficient depth is obtained there is no sense in administering further anesthetics. In general an overdose of anesthetics has only damaging effects and therefore has to be avoided.

In the medical world it is generally accepted that the sensitivity for the effects of the various anesthetics shows a large degree of intra-individual and interindividual variation for human beings and for animals. One tries in practice to adapt the dose of anesthetics to the individual need. Important basic data for selecting the dose are the weight, age and health condition of the individual. The influence of an anesthetic on the central nervous system and especially the depth of the anesthesia, obtained by means of a predetermined dose of the anesthetic, is, however, not measurable and in practice the experience of the anesthesiologist will play an important role in determining the dose of anesthetics.

During general anesthesia there is no reference site left and the patient is not able to tell anything or signal anything to the anesthesiologist, so the above-described prior art system cannot be used for quantifying the effect of the used general anesthetic.

An object of the invention is to provide a system and a method for quantifying the general anesthetic effect of general anesthetics on a human or an animal, and especially a system with the capability to determine the anesthesia depth in reproducable manner and independent of the cardiovascular condition of the human

or animal in such a manner that an unambiguous relation can be determined between the applied dosis of anesthetics and the anesthetic effect resulting therefrom.

Also in the research environment there is a need for a reliable system to test the general anesthetic effect or influence of certain anesthetics in an accurate and reproducable manner. Therefore a further object of the invention is to provide a system and method by means of which the general anesthetic influence of certain anesthetics on a human or an animal can be measured in a reproducable manner and independent of the cardiovascular condition of the respective human or animal.

In agreement with these objects the invention now provides a system of the type, described in the heading paragraph of this description, which in agreement with the invention is characterized in that

- the anesthetic of which the effect is to be quantified is a general anesthetic the purpose of which is to temporarely decrease those functions of the central nervous system which together determine the function "awareness" of the central nervous system,
- the first means are embodied as one or a restricted number of stimulus transmitting elements destined to stimulate a specific sensor which in response thereto will cause the central nervous system to a specific response the strength of which being representative for the function "awareness" of the central nervous system,
- the second means are embodied to control said first means for sequentially transmitting stimuli of constant strenght, said strength being adjusted to a level causing under full awareness circumstances a response which is percieved bearable by the human or animal,
- the third means are embodied and positioned on the body of the human or animal to detect the strength of said specific evoked respons and to generate a strength dependent detection signal,
- the fourth means are embodied to carry out the following functions:
  = memorize the strength of at least one detection signal

corresponding to a response evoked in the body of the human or animal before any anesthetic is administered to the body of the human or animal

= compare the strength of said at least one memorized detection signal with the strength of every detection signal corresponding to a response evoked after the start of administering an anesthetic to the body

= indicating the result of said comparison,

whereby the stimuli are selected such that the response thereon starts and ends within a predetermined time interval.

The system according to the invention is based on a twofold idea. The first part of the idea is that the functional condition of the central nervous system can be determined by measuring the input-output relation, whereby the input concerns the stimulation of the efferent nerves and the output concerns the activation of an end organ by afferent nerves. The second part of the idea is that the functional condition of the central nervous system will be modified by general anesthetics. This twofold idea has lead to the understanding that the functional condition of the central nervous system can be quantified by directly measuring the response which is caused by applying stimuli, especially stimuli which will lead to a time restricted response, so that the measurement is very well quantifyable and is repeatable. Therewith a method can be realized which is independent of the circulative condition, the age, the weight or other subjective parameters which are different for each human being or each animal.

Stimuli can be applied in various manners. A first specific embodiment of the system according to the invention is in this respect characterized in that the first means are embodied as one single electrical electrode and that the second means are embodied to generate electrical signals to said electrode. Another specific embodiment of the system according to the invention is characterized in that thefirst means are embodied as one single pressure transmitting electrode and that the second means are embodied to generate pressure signals to said electrode.

It is remarked that as such the application of predetermined stimuli on which a specific response can be expected is a well-known technique within the medical world.

Pressure pulse generators, for instance comprising piezo-electric transducers, mechanical pressure bars, etc. are also known themselves and do not need further explanation.

The response to the stimuli can be of a different nature and dependent on the nature of the response the third means have to be selected such that predetermined parameters of the response can be quantified. A specific embodiment of the system according to the invention is in this respect characterized in that the third means are embodied and positioned in relation to the body of the human or animal to detect a movement of a certain body part of the human or animal, for which purpose the third means comprise a movement detector cooperating during operation of the system with said predetermined body part.

Another specific embodiment of the system according to the invention has the characteristic that the third means are embodied and positioned to detect the electrical impedance of a predetermined body part of the human or animal, for which purpose the third means comprise an impedant measuring circuit which during operation of the system is coupled to said predetermined body part of the human or animal.

Although the administeration of anesthetics can be controlled by hand during operation of the system, for instance such that an anesthesiologist on the one hand administers predetermined relatively small dosis of anesthetics to the human or animal and on the other hand monitors the effect thereof using the system according to the invention, it is also possible to create a feedback in the control circuit by adding fifth means which are embodied to be controlled by the ratio dependent control signal generated by the fourth means such that said fifth means are activated to administer predetermined doses of anesthetic as the ratio represented by said control signal is above a predetermined treshold value and are deactivated as the ratio represented by said control signal is underneath said treshold value.

In fact the human being or the animal, which receives the stimuli from the first means and whose response is monitored by said third means forms an essential part of the whole control circuit. Those parts of the circuit which are destined for applying the stimulus (the first means) are coupled to or cooperate together

with the afferent part of the nervous system of the human being or the animal and the response monitoring means (third means) are coupled to that part of the body of the human being or the animal where the response to said stimilus is expected, which response is initiated in the central nervous system and activates the efferent nerves. Therefore the central nervous system acts as intermediate component between the first and the third means within the control circuit.

A specific embodiment of the system, especially for testing of anesthetics has the characteristic that the system comprises a test animal such as a mouse or a rat, which test animal during use of the system receives stimuli generated by said second means and applied through said first means, whereby the evoked response in the body of the test animal is detected by said third means and whereby one or more parameters of said response are quantified by said fourth means.

Above special attention is paid to the use of stimuli in the form of electrical signals or pressure signals. However, in principle also other stimuli can be used, such as stimuli induced by temperature (cold or warmth), noise or radiation (light). These other forms of stimuli are not always definable in a measurable configuration and will not always result into an unambiguous and easy to measure response and therefore in most cases electric stimuli or pressure stimuli are preferred although the invention is not restricted thereto. Much of the stimuli can be classified as noxious stimuli, such as for instance the stimuli caused by a temperature difference. The nervous system of the human or animal will react to said noxious stimuli by a withdrawal response, in other words the central nervous system will react to noxious stimuli by moving that body part of the human or animal, which is exposed to said noxious stimuli, in such a manner that the respective body part is moved out of the influencial range of the noxious stimuli. Especially such withdrawal reflexes are preferably applied within the scope of the invention, whereby it is assumed that the strength of the withdrawal reflex of the human or animal which is under the influence of anesthetics, is dependent on the momentaneous anesthesia depth.

The invention is further supported by the understanding that

it is not necessary to actually apply a noxious stimulus to the human or the animal, but that it is sufficient to input therewith corresponding electrical stimulus or a stimulus of another nature at a suitable position through suitable afference into the nervous system of the human being or the animal.

The invention will be explained in more detail with referencemeans and applied through said first means, whereby the evoked to the attached drawings.response in the body of the test animal is detected by said third

Figure 1 illustrates schematically a first embodiment of ameans and whereby one or more parameters of said response are system according to the invention.quantified by said fourth means.

Figure 2 illustrates the system in figure 1 shown in the form of a control process.

Figure 3 illustrates the response change of the central nervous system as function of time when a certain dose of anesthetic is applied.

Figure 4 illustrates the relation between the applied doses of anesthetic and the therewith obtained anesthetic effect.

Figure 5 illustrates the possibile progress of an anesthesia as monitored and controlled by the system according to the invention.

Figure 6 illustrates the form a control process a second embodiment of a system according to the invention including a feedback to the anesthesia-application apparatusses.

Figure 7 illustrates the relation between the stimulus strength and the response strength for varying doses of anesthetic.

Figure 8 illustrates a third embodiment of the system according to the invention, especially destined for researching the anesthetic working of certain chemical compounds.

Figure 1 illustrates schematically a possible embodiment of a system according to the invention. The system comprises an electrode 10 which through a lead 11 is connected to a signal generator 12. The electrode 10, which is known as such, is suitable for transcutaneous electrical stimulation of a part of the human body. In the illustrated example the electrode 10 is positioned on the schematically illustrated lower arm 13 of a further not illustrated human being. The signal generator 12 is destined to

generate stimuli in the form of electric pulses or pulse series, which are dimensioned such that during the application thereof through the electrode to the body of the human being a certain noxious stimulus is simulated. The application of such stimuli and the shaping of suitable electric pulses or pulse series is considered as known to the expert in this field. Also the components 10, 11 and 12 are considered as known to the expert so that any further explanation is superfluous.

The system according to the invention comprises furthermore a movement detector 14 which is connected through a suitable lead to a processor 17. Each movement of the finger 15 is translated by said movement detector 14 in an electrical signal which through a lead 16 is transferred to the processor 17. In the processor 17 the received signals are processed in a manner which will be described in more detail and are evaluated in such a manner that a value can be made visible on the indication unit 18 forming a measure for the anesthetia depth. The value on the indication unit 18 may vary for instance between 0 and 100%, whereby 0% for instance indicates the total absence of any form of anesthetia, whereas 100% indicates the situation in which no reaction is measurable after application of a stimulus.

The movement detector 14 can be embodied in various ways. Known movement detectors use for instance a small Doppler radar transmitter which is directed to that part of the body of which the movement has to be detected. Such a movement detector delivers at the output of the receiver both information concerning the amplitude of the movement as well as information about the speed of the movement. Other known movement detectors use for instance strain gauges which are adhered to that body part of the human or animal which is to be monitored and by means of which the tension in said body part, developed when a withdrawal reaction is carried out, can be measured. As such these movement detectors are known and a further illustration of this detector is considered superfluous.

During use of the system the signal generator 12 is adjusted such that therewith certain pulses or pulse series can be generated which, through the lead 11 and the electrode 10, can be applied to the arm 13 of the human to stimulate in there certain afference. In

the figure 10 schematically an afferent nerve 9 is drawn, which can be stimulated by the electrode 10 and will transport thereafter a signal to the central nervous system, which is schematically indicated within the dashed line 8. In response to the received signal the central nervous system 8 will transmit a signal through the also schematically indicated efferent outgoing nerve 7, by means of which the muscles connected to the finger 15 are activated in such a manner that more specifically the finger 15 will bend. This bending movement of the finger 15 will be detected by the movement detector 14, which in turn will supply a signal, corresponding to the strength of the movement or the amplitude of the movement through the lead 16 to the processor 17. In a very simple embodiment of the system the processor 17 determines the strength of the electric signal and takes the necessary steps to visualize a therewith corresponding value, preferably normalized between the 0% and 100% boundaries onto the indicator unit 18.

Not only the pulses or pulse series, generated by the signal generator 12 are dimensioned and shaped in such a manner that the desired response of a certain body part is obtained. Also the signals are shaped in such a manner that the response is restricted in time. In the underlying situation that implies especially the bending movement of the finger 15 will last for some seconds or even only a part of a second, whereafter the finger will relax and will return back to the same position as before the electrical pulse series was applied.

If now during this measuring process a pharmacon or anesthetic is administered to the human, for instance through inhalation or through intraveneus injection, then as result thereof the response of the central nervous system will decrease. In other words, as more anesthetic is applied the withdrawal reflex, in the described example the bending movement of the finger 15, will gradually decrease and therefore also the signal which is delivered by the movement detector 14 through the lead 16 to the processor 17 will decrease in amplitude. The anesthesiologist may draw conclusions from the indicated value on the indicator 18 about the obtained momentaneous anesthesia depth and may draw conclusions about the eventual further administering of anesthetics.

Figure 2 illustrates the system in figure 1 in another

manner, such that it will be clear that in the system according to figure 1 in fact a control process is carried out. In figure 2 the components corresponding to components in figure 1 are indicated with the same reference numbers. The generator 19 generates stimulation signals which through the lead 11 are supplied to the electrode 10. The electrode 10 causes the stimulation of the afferent nerve(s) 9 and through said nerve 9 the signal will be transferred to the central nervous system 8. In the central nervous system 8 the received signal is processed with the result that through the efferent nerves 7 certain muscles are activated which will cause the bending movement of the finger 15. This movement is detected by means of the movement detector 14. The detector 14 will transfer a signal through the lead 16 to the processor 17 which processor is combined with the indication unit 18. The output signal of the processor 17, visible on the indication unit 18, is observed by an anesthesiologist 20. The transfer of information from the indication unit 18 to the anesthesiologist 20 is indicated by means of the dashed line 19. The anesthesiologist 20 operates an apparatus 22 for applying anesthetics. The fact that the apparatus 22 is controlled by the anesthesiologist 20 is indiced by the dashed line 21. The applied anesthetic will influence the functioning of the central nervous system 8 and this influence is schematically indicated in figure 2 by means of the arrow 23.

Figure 3 illustrates the variation of the response of the central nervous system in case only once a predetermined dose of a certain anesthetic is administered to the human or animal. The horizontal axis in figure 3 represents the time and the vertical axis is marked with the response strength, which varies between 0% (no response at all) and 100% (a complete response). Before the time t1, in other words left of t1 on the time scale, no anesthetic is administered. If with regular intervals stimuli are applied by means of the generator 12 and the electrode 10 then, as is indicated by the vertical response strength lines, each time a response of 100% will be measured by the processor 17. The actual response strength may differ for each individual, however, the measured response before the time t1 will be set to 100%. At the time t1 a predetermined dose of anesthetic (dose 1) will be administered and as reaction thereon the response will decrease in

a relatively fast rate, as appears from figure 3. At the time t2 in fact the minimal response is obtained which, related to the 100% value before the time t1 is now equal to a%. From that time onwards the influence of the anesthetic will gradually decrease so that at the time t3 again a 100% response is observed. The angle of the slope of the response variation between t1 and t2 and also the angle of the slope of the response variation between t2 and t3 depends on the used pharmacon or anesthetic and also depends on the individual.

It will be clear furthermore that with another dose also another response variation will be observed. As example in figure 3 the variation for a relatively smaller dose 2 is indicated. The minimal response for dose 2 appears to be b%. There is also a certain dose which will lead to a response of 0%. If the strength of the dose is increased further then the response will be maintained at 0%, however, as is mentioned above, further noxious effects will appear which are very undesirable.

Figure 4 illustrates the relation between the dose strength of the administered anesthetic and the response respectively the obtained effect. For a definition of the term "effect" the following formulas are used:

$$\text{response (\%)} = \frac{\text{withdrawal reflex during anesthesia}}{\text{withdrawal reflex without anesthesia}} \times 100$$

$$\text{effect (\%)} = 100 - \text{response (\%)}$$

For a human which does not have received any anesthetics the response will be 100% and the effect therewith will be 0%. If anesthetics are administered then the response will decrease and the desired effect of the anesthetic will increase in an inverted proportional manner. At the moment no response is received anymore the 100% effect will be obtained. As soon as this situation is reached further administering of anesthetics to increase the effect does not have any useful purpose and may only lead to disadvantage consequences.

As appears from figure 4 the relatively strong dose 1 in the example of figure 3 will result into a low response of a% and inversely proportional therewith in a relatively strong effect of 100-a%. The relatively weaker dose 2 in the example of figure 3

results into a response of b% and a therewith corresponding effect of 100-b%. Figure 4 shows that the relation between effect and dose is represented in general by an S-shaped curve. On the grounds of the already above-mentioned analgetic and circulatory effects the exact position of this S-shaped curve is not identical for each individual. The effect curce 30, illustrated in full line, corresponding to the response curve 32, may apply to a first individual, whereas the effect curve 31, illustrated by a dashed line, may apply to another individual. However, it is true that the S-shape of the curve is universally valid irrespective of the exact positioning of said curve. That implies that for each individual in principle only two measurements with two different doses are necessary to be able to draw the dose-effect-curve for the respective individual and for the used pharmacon or anesthetic. In other words, as soon as two points of the S-shaped dose-effect-curve are known in the processor 17 and the general shape of the curve is in a suitable manner stored in the processor 17, then this processor 17 is able to calculate the actual curve for the individual to be treated, at least within certain tolerance boundaries.

For a good understanding it is remarked that it is not always necessary to obtain a 100% anesthesia depth. Depending on the circumstances the anesthesiologist may for instance decide to strive for a 70 or 80% effect. Under the guidance of the obtained effect the effect level can be maintained by regularly administering small doses of anesthetics and as soon as no anesthetics are administered anymore the recovery process will start.

In figure 5 schematically the progression of a possible anesthesia is indicated whereby, viewed in time, the whole treatment can be subdivided into an initiatory phase between t1 and t2, a level phase between t2 and t3 and a recovery phase between t3 and t4. (For the sake of clearness it is remarked that the separate responses, which together determine the illustrated curve, are not shown individually as is done in figure 3). At the moment t1 a first dose of anesthetic is administered, causing the response to show a strong decrease. As appears from figure 5 this dose was not sufficient to obtain the desired response level of c%. By adding a

small extra dose at the time t2 the desired level of c% was obtained. From that moment on the desired level response of c% was maintained by administering small extra doses until the time t3. At the time t3 the recovery phase starts. During this phase no anesthetic is administered anymore and the response will gradually increase until the 100% level is reached again at the time t4. This whole anesthesia can be monitored and controlled by the system according to the invention. Preferably the system in figure 2 is further developed into the embodiment which is illustrated in figure 6.

In the embodiment of figure 6 all components which correspond to those in the embodiment of figure 2 are indicated by the same reference numbers. The difference between the figures 2 and 6 is in fact the direct control of the anesthetic administeration unit 22 by the processor 17. This is indicated in figure 6 by the direct connection 24 through which control signals are supplied from the processor 17 to the unit 22. The interaction between the anesthesiologist 20 and the processor 17 is symbolized by the connection 25. The anesthesiologist 20 determines when the anesthesia should start (time t1) and indicates the base line level (c%) to be obtained. As soon as these data are inputted in the processor 17 the system is able to carry out the anesthesia automatically and it is sufficient for the anesthesiologist 20 to monitor the data on the indication unit 18 presented by the processor 17 to control the course of the anesthesia. As soon as the administering of anesthetics can be terminated (time t3) a thereto related command is inputted by the anesthesiologist 20 into the processor 17 which in response will stop the administeration of anesthetic through the administration unit 20. In the following phase the system according to the invention can be used to monitor the behaviour of the human or animal during the recovery phase of the anesthesia.

The system according to the invention can not only be used in the above described manner during the administeration of an anesthetic to apply non-varying stimuli and to monitor by means of the processor 17 and the indicator unit 18 the variation of the response of the central nervous system dependent on the momentary dose of the anesthetic. It is also possible to observe the response

on a varying stimulus in the presence of a predetermined anestnatic dose, especially a gradually increasing stimulus. The relation between the stimulus strenght and the response strength is for two different doses schematically indicated in figure 7, whereby as reference also the situation without any anesthetic is illustrated.

As is remarked above the system according to the invention is not only suited to be used by an anesthesiologist as a means for administering the correct dose of anesthetic to obtain a desired anesthesia depth, but is also suited to be used in a research environment for testing the anesthetic working of certain chemical compounds.

An embodiment which is especially developed for that purpose is illustrated in figure 8.

The embodiment in figure 8 comprises a resting place 50 for a test animal 51, in the illustrated embodiment being a mouse or a rat. The test animal 51 is fixed on the resting place 50 by connecting one end of a hooked bar 52 to the upper teeth of the test animal 51 and by connecting the other end thereof to the fixed column 53. Furthermore a wire 54 is on the one hand through a band 55 connected to the tail root of the rat 51 and is on the other hand connected to a fixed column 56. By means of the hooked bar 52 and the wire 54 the test animal 51 is maintained in position on the resting place 50. It will be clear that also other means can be used to fix the test animal in position. Such means are considered as known to the expert in this field.

In the manner illustrated in figure 8 an electrode assembly 57 is connected to one of the hind legs of the rat 51. This electrode assembly 57 is through leads 58 connected to the electrical signal generator 59. The same hind leg of the rat 51 is through a connection 60 coupled to a power transducer 61 which is attached at a fixed position to the column 62. The transducer 61 produces electrical signals which through the leads 63 are supplied to the processor 64.

In the illustrated embodiment of the system furthermore an breathing hose 65 is shifted within the mouth of the test animal 51. Through the valve 66 a mixture of air, supplied through the conduit 67 and anesthetic, supplied through the conduit 68, can be administered to the test animal.

The system may eventually comprise further means for measuring and controlling the body temperature of the test animal, means for measuring and controlling the blood pressure, hard rate and other parameters, which may play a role during the investigation. These means are, however, not considered as essential within the scope of the invention and are therefore not illustrated in the figure.

It will be clear that the system which is illustrated in figure 8 may function in the same way as the system illustrated in the figures 1, 2 and 6. The anesthetic can be administered for instance in the form of a gas by means of the components 65....68. However, it is also possible to intraveneus administer the anesthetic in which case the components 65.....68 should be replaced by suitable means therefore which are considered known as such. Both before the anesthesia as well as during the administeration of anesthetic pulses or pulse series with predetermined shape and dimensioning can be generated in the generator 59 and supplied through the electrodes 57 to the hind leg of the rat 51. These pulses will through the afferent nerves get access to the central nervous system of the rat 51, whereby after propagation of the pulses, processing thereof in the central nervous system a withdrawal reflex will result in the same hind leg, which withdrawal reflex is measured by the power transducer 61. The measured strength of the withdrawal reflex is in the form of an electrical signal supplied through the leads 63 to the processor 64 in which the measured strength is stored and eventually further processed. The result of the signal processing can be made visible through the indication unit.

Also in the case of the embodiment of figure 8 it is possible to realize a coupling between the means for administeration of the anesthetic and the processor 64 in such a manner that a feedback control circuit is obtained.

Although in figure 8 very schematically a processor 64 and a generator 59 are illustrated it will be clear that in more sophisticated embodiments the processor may take the form of a computer or data logger by means of which data from a number of signal sources, not only the sources of the above-mentioned second means, but for instance also signals which are representative for

the body temperature, blood pressure, hard rate etc. can be received, stored and eventually directly processed by means of special purpose software. Such data acquisition systems are known as such and do not require any further explanation.

Above special attention is paid to the system according to the invention. However, the invention is also related to a method and more specifically to a method for determining the influence of an anesthetic on the functioning of the central nervous system of a human or animal, in case predetermined relatively small doses of the respective anesthetic are administered to a human or animal at predetermined time distances. The method according to the invention comprises the following steps:

- a predetermined stimulus is transmitted to the input side of the nervous system of the human or animal,
- said stimulus is transmitted periodically in a controlled manner,
- the response evoked in the body of the human or animal as result of each applied stimulus is detected and at least one parameter of said response is quantified, the series of quantified parameters is processed to obtain an indication of the anesthetic effect,

whereby

- the stimuli have a constant strenght, said strength being adjusted to a level causing an evoked response which is perceived bearable, whereby the stimuli are selected such that the response thereon starts and ends within a predetermined time interval,
- the processing of the quantified parameters is doen by carrying out the following functions:
  - = store the quantified parameters corresponding to a response evoked in the body of the human or animal before any aneasthetic is administered to the body of the human or animal
  - = compare the strength of every quantified parameter corresponding to a response evoked after the start of administring an aneasthetic to the body with the at least one stored signal strength
  - = indicating the result of said comparison.

CLAIMS

1. System for quantifying the anesthetic effect of anesthetics on a human or an animal, comprising

- first means for transmitting a predetermined stimulus to the input side of the nervous system of the human or animal,
- second means for activating said transmitting means in a controlled manner,
- third means for detecting the response evoked in the body of the human or animal as result of each transmitted stimulus and for generating a thereto corresponding signal,
- fourth means for processing the signals generated by said third detecting means,

characterised in that

- the anesthetic of which the general anesthetic in effect is to be quantified is a general anesthetic the purpose of which is to temporarily decrease those functions of the central nervous system which together determine the function "awareness" of the central nervous system,
- the first means are embodied as one or a restricted number of stimulus transmitting elements destined to stimulate a specific sensor which in response thereto will cause the central nervous system to a specific response the strength of which being representative for the function "awareness" of the central nervous system,
- the second means are embodied to control said first means for sequentially transmitting stimuli of constant strenght, said strength being adjusted to a level causing under full awareness circumstances a response which is perceived bearable by the human or animal, whereby the stimuli are selected such that the response thereon starts and ends within a predetermined time interval,
- the third means are embodied and positioned on the body of the human or animal to detect the strength of said specific evoked respons and to generate a strength dependent detection signal,
- the fourth means are embodied to carry out the following functions:

= memorize the strength of at least one detection signal corresponding to a response evoked in the body of the human or animal before any anesthetic is administered to the body of the human or animal

= compare the strength of said at least one memorized detection signal with the strength of every detection signal corresponding to a response evoked after the start of administering an anesthetic to the body

= indicating the result of said comparison.

2. System for quantifying the effect of anesthetics on a human or an animal, comprising

- first means for transmitting a predetermined stimulus to the input side of the nervous system of the human or animal,
- second means for activating said transmitting means in a controlled manner,
- third means for detecting the respons evoked in the body of the human or animal as result of each transmitted stimulus and for generating a thereto corresponding signal,
- fourth means for processing the signals generated by said third detecting means,
- fifth means for administering an anestetic to the body of the human or animal,

characterised in that

- the anesthetic of which the general anesthetic effect is to be quantified is a general anesthetic the purpose of which is to temporarely decrease those functions of the central nervous system which together determine the function "awareness" of the central nervous system,
- the first means are embodied as one or a restricted number of stimulus transmitting elements destined to stimulate a specific sensor which in response thereto will cause the central nervous system to evoke a specific response the strength of which being representative for the awareness of the central nervous system,
- the second means are embodied to control said first means for sequentially transmitting stimuli of constant strenght, said strength being adjusted to a level causing under full awareness circumstances an evoked response which is perceived

bearable by the human or animal, whereby the stimuli are selected such that the response thereon starts and ends within a predetermined time interval,

- the third means are embodied and positioned on or near the body of the human or animal to detect the strength of said specific evoked respons and to generate a strength dependent detection signal,
- the fourth means are embodied to carry out the following functions:
  - = memorize the strength of at least one detection signal corresponding to a response evoked in the body of the human or animal before any anesthetic is administered to the body of the human or animal
  - = compare the strength of said at least one memorized detection signal with the strengt of every detection signal corresponding to a response evoked after the start of administering an anesthetic to the body,
  - = generating a ratio dependent control signal to the fifth means,
- said fifth means are embodied to be controlled by said ratio dependent control signal such that said fifth means are activated to administer predetermined doses of anestetic as the ratio represented by said control signal is above a predetermined threshold value and are deactivated as the ratio represented by said control signal is underneath said threshold value.

3. System according to claim 1 or 2, characterized in that the first means are embodied as one single electrical electrode and that the second means are embodied to generate electrical signals to said electrode.

4. System according to claim 1 or 2, characterized in that the first means are embodied as one single pressure transmitting electrode and that the second means are embodied to generate pressure signals to said electrode.

5. System according to one of the precedig claims, characterized in that the third means are embodied and positioned in relation to the body of the human or animal to detect a movement of a certain body part of the human or animal, for which purpose the third means

comprise a movent detector cooperating during operation of the system with said predetermined body part.

6. System according to one of the claims 1-4, characterized in that the third means are embodied and positioned to detect the electrical impedance of a predetermined body part of the human or animal, for which purpose the third means comprise an impedant measuring circuit which during operation of the system is coupled to said predetermined body part of the human or animal.

7. System according to one of the preceding claims, characterized in that the fourth means comprise a processor, programmed to carry out the mentioned functions of the fourth means.

8. System according to one of the preceding claims, characterized in that the system comprises auxiliary means on which the human or animal can be maintained in a predetermined position during the anesthesia.

9. System according to claim 8, characterized in that the system comprises a test animal such as a mouse or a rat, which test animal during use of the system receives stimuli generated by said second means and applied through said first means, whereby the evoked response in the body of the test animal is detected by said third means and whereby one or more parameters of said response are quantified by said fourth means.

10. Method for quantifying the graded effect of anesthetics on a human or an animal, according to which

- a predetermined stimulus is transmitted to the input side of the nervous system of the human or animal,
- said stimulus is transmitted periodically in a controlled manner,
- the response evoked in the body of the human or animal as result of each applied stimulus is detected and at least one parameter of said response is quantified, the series of quantified parameters is processed to obtain an indication of the anesthetic effect,

characterised in that

- the stimuli have a constant strenght, said strength being adjusted to a level causing an evoked response which is perceived bearable, whereby the stimuli are selected such

that the response thereon starts and ends within a predetermined time interval,

- the processing of the quantified parameters is doen by carrying out the following functions:
  - = store the quantified parameters corresponding to a response evoked in the body of the human or animal before any aneasthetic is administered to the body of the human or animal
  - = compare the strength of every quantified parameter corresponding to a response evoked after the start of administring an aneasthetic to the body with the at least one stored signal strength
  - = indicating the result of said comparison.

Fig-1

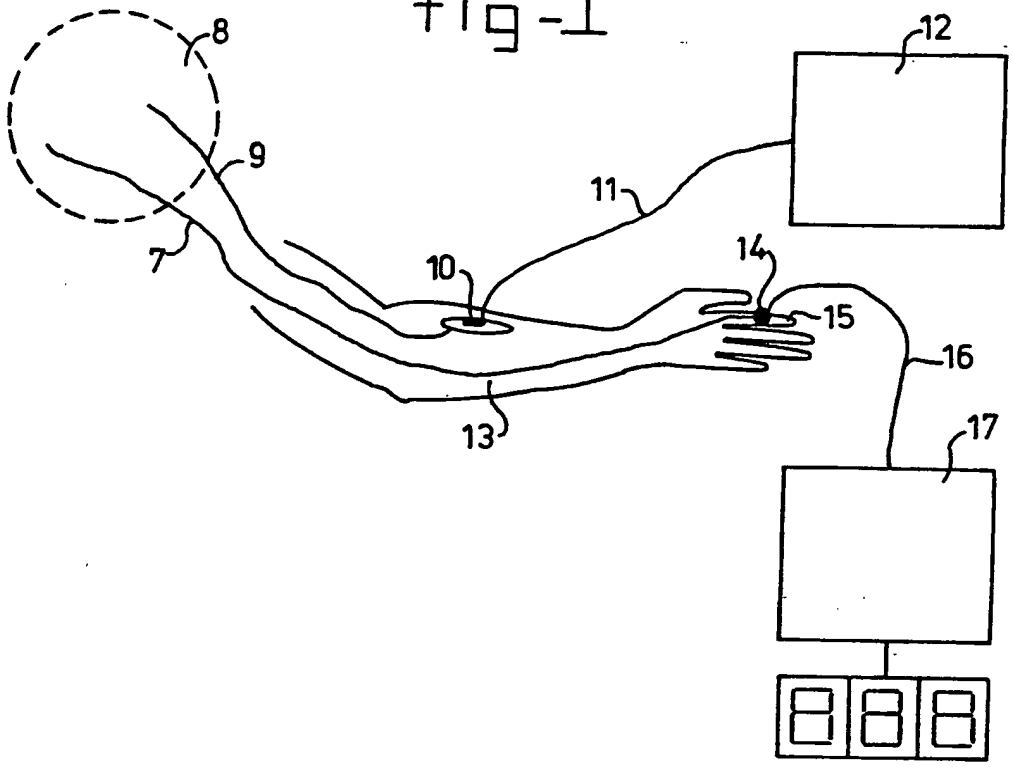


Fig-2

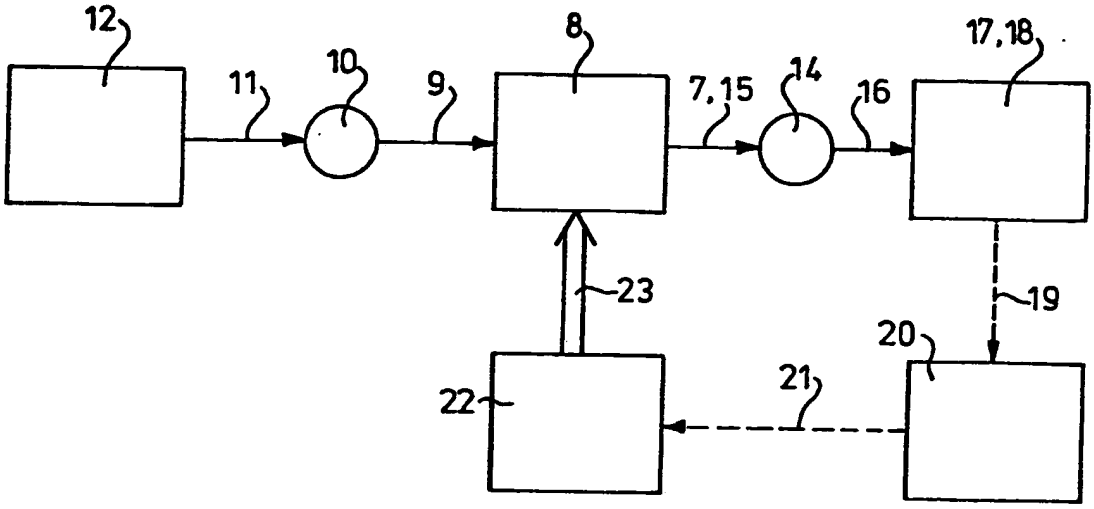
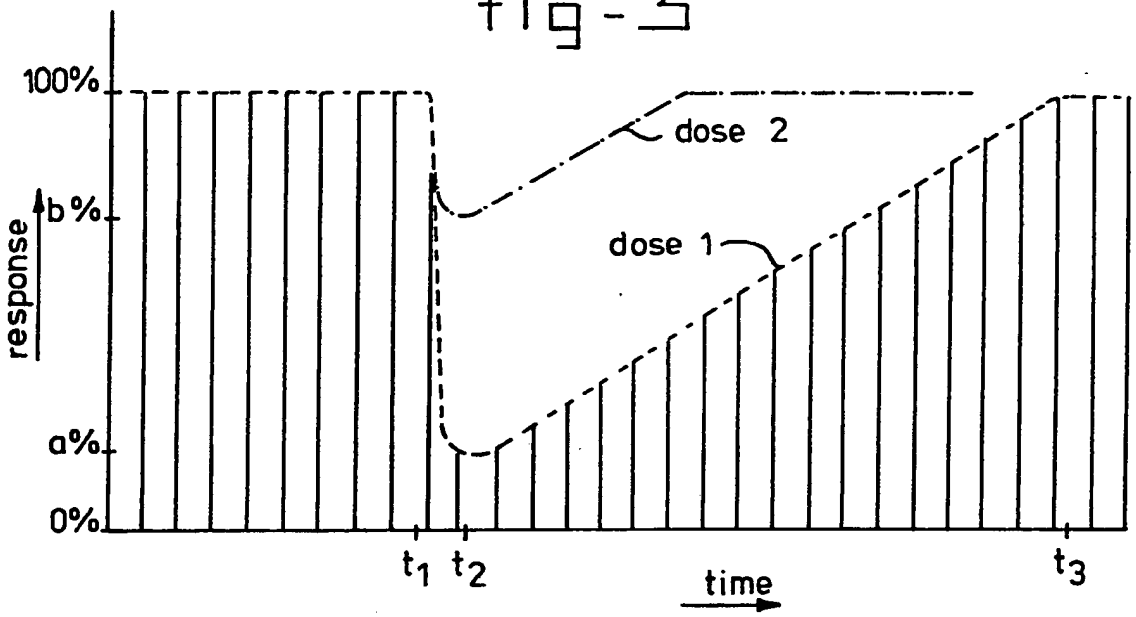


Fig-3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b%
response
a%
0%
dose 2
dose 1
t_1 t_2
time
t_3

Fig-4

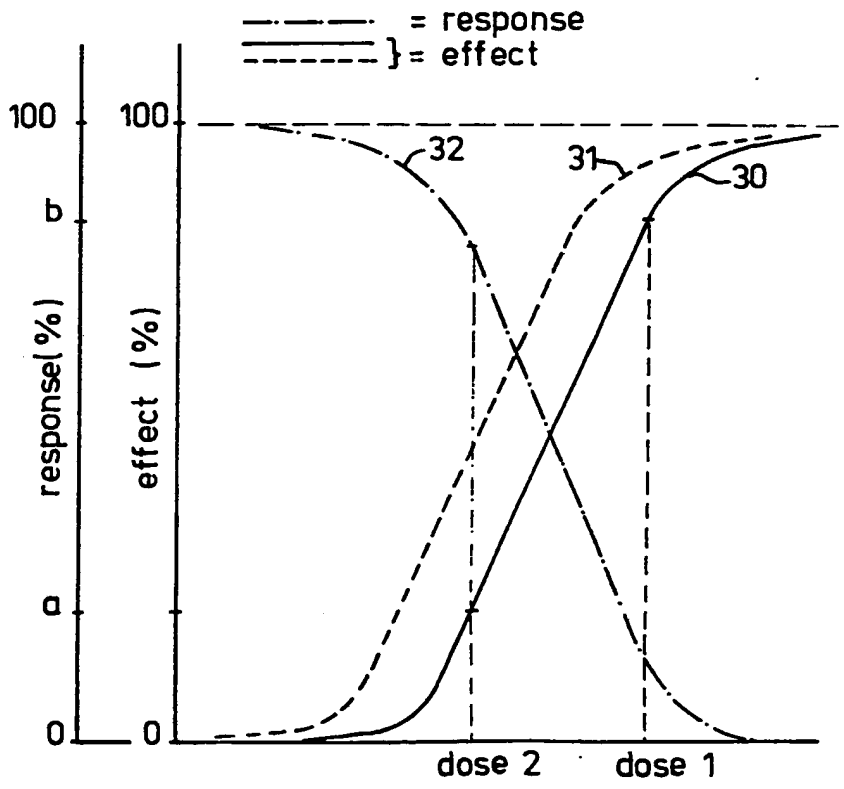
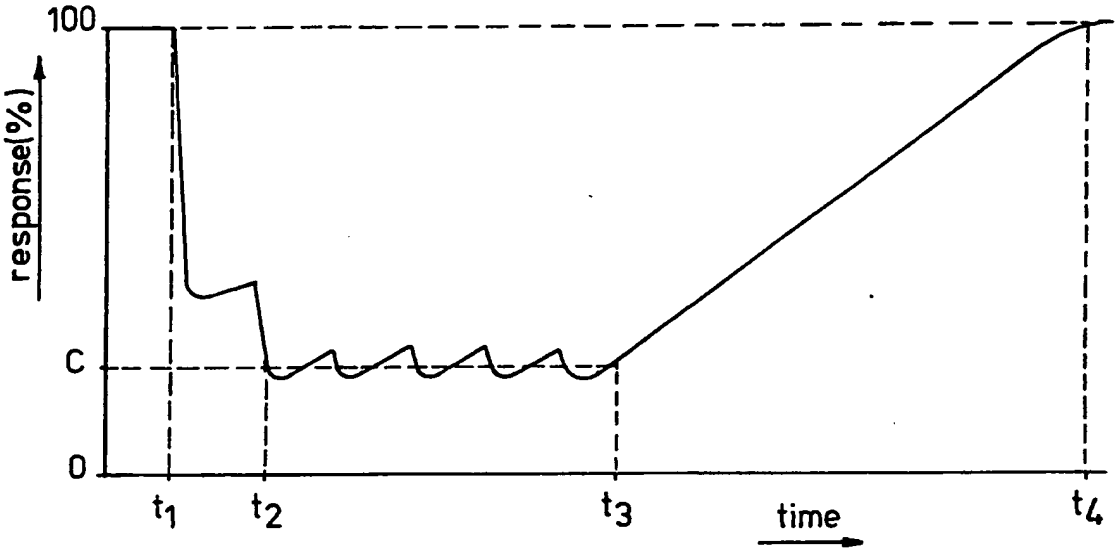

= response
} = effect
100
100
b
a
0
0
response(%)
effect (%)
32
31
30
dose 2
dose 1

Fig-5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response(%)
C
0
t1
t2
t3
time
t4

Fig-6

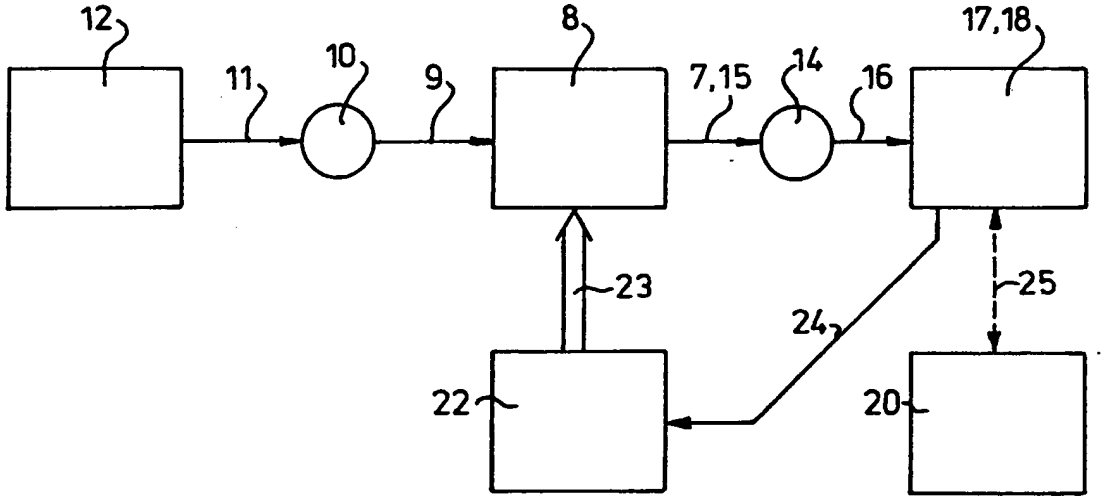
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Fig-7

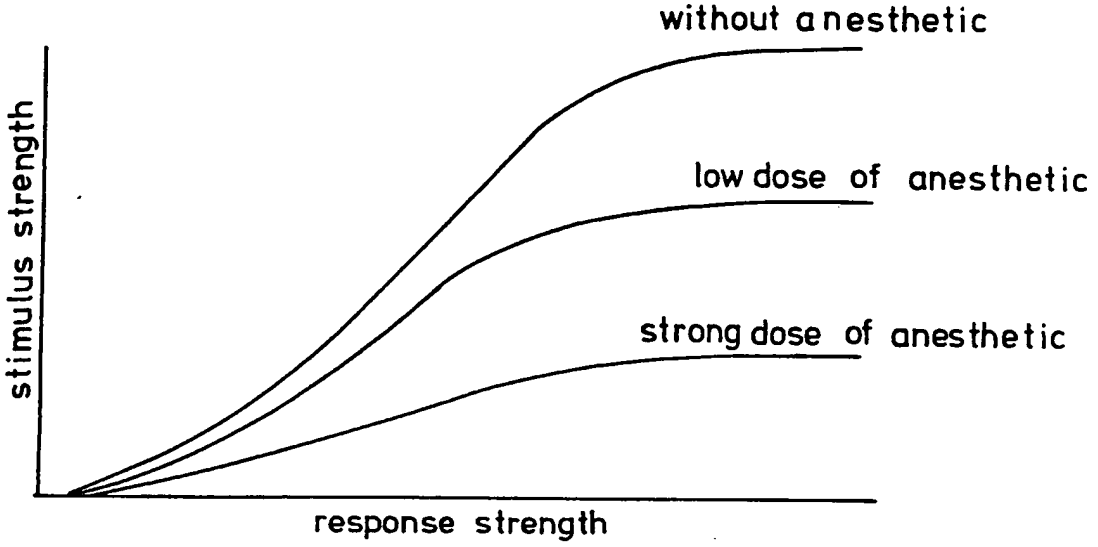
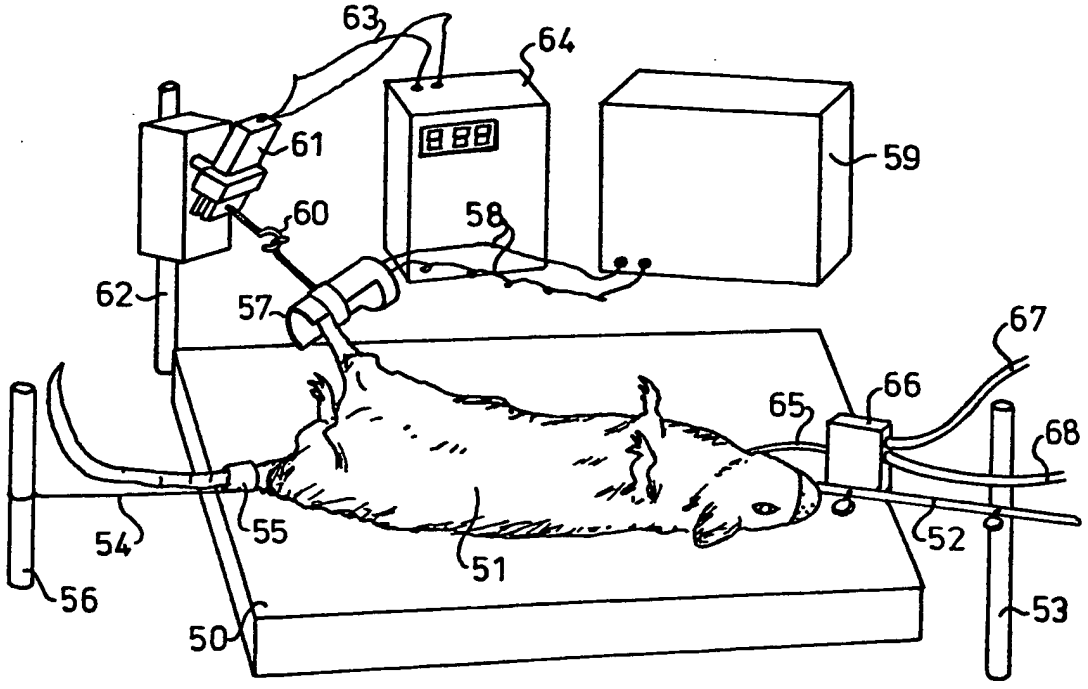

without anesthetic
low dose of anesthetic
strong dose of anesthetic
stimulus strength
response strength

Fig-8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INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 91/00067

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61B9/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61B ; A61N

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	US,A,4570640 (J.E.BARSA) 18 February 1986 see the whole document	1-4, 10
A	(cited in the application)	5-7
Y	SOVIET INVENTIONS ILLUSTRATED Section P/Q, week 8640, 15 February 1986 Derwent Publications Ltd., London GB Accession No. 86-263267/40 & SU-A-1210779 ; 15 February 1986 see the abstract	1-4, 10
A	US,A,4759377 (D.D.DYKSTRA) 26 July 1988 see abstract; figures 1-3	1, 4, 5, 7
A	WO,A,8502333 (BIOKINETICS INC.) 06 June 1985 see abstract; figures 1-7	1, 4

-/--

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 JULY 1991	05.08.91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HUNT B.W.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	MEDICAL AND BIOLOGICAL ENGINEERING AND COMPUTING. vol. 23, no. 6, November 1985, STEVENAGE GB pages 547 - 555; H.S.Bradlow et al.: "Microcomputer-based muscle relaxation monitor and controller for clinical use" see the whole document ---	1-3, 5, 7
A	EP,A,283387 (BIO INDUSTRY SARL) 21 September 1988 see abstract; figures 1-3 ---	1, 5
A	US,A,4387723 (J.L.ATLEE III ET AL.) 14 June 1983 see abstract; figures 1-6 ---	1-3, 5, 7
A	DE,A,3146446 (BIODEC INC.) 18 November 1982 see abstract; figures 1-8 ---	8, 9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. NL 9100067

SA 46765

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 18/07/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US-A-4759377	26-07-88	None	
WO-A-8502333	06-06-85	US-A- 4711248	08-12-87
		AU-A- 3745785	13-06-85
		EP-A- 0163732	11-12-85
EP-A-283387	21-09-88	FR-A- 2612069	16-09-88
		FR-A- 2612068	16-09-88
		US-A- 4848359	18-07-89
US-A-4387723	14-06-83	None	
DE-A-3146446	18-11-82	US-A- 4386613	07-06-83
		JP-A- 57156558	27-09-82